Fingolimod-Associated Macular Edema (FAME) in the Treatment of Multiple Sclerosis

Fingolimod, a major treatment for Multiple Sclerosis, can cause macular edema within four months of treatment onset. Fingolimod-Associated Macular Edema can present asymptomatically and generally resolves with good visual prognosis after drug cessation.

I. Case History

- Patient demographics:
  - 61 year old, white male
- Chief complaint:
  - none, comprehensive eye exam
- Medical history:
  - Multiple Sclerosis (MS)
    - Relapsing-Remitting classification
    - Diagnosed 3 years prior to initial presentation
  - Hypertension (HTN)
  - Coronary Artery Disease (CAD) with myocardial infarction (MI)
  - Dyslipidemia
  - Depression
  - Spasticity
- Medications:
  - MS: baclofen, fingolimod (FTY720/Gilenya®; Novartis Pharmaceuticals, East Hanover, New Jersey), teriflunomide
  - HTN: amlodipine, lisinopril, metoprolol
  - CAD with MI: aspirin
  - Dyslipidemia: atorvastatin
  - Depression: bupropion, methylphenidate
  - Spasticity: botox injections
- Ocular history:
  - Dry eyes, refractive error

II. Pertinent Findings

Comprehensive Eye Exam (Initial Presentation)

- Exam Findings:
  - Best Corrected Visual Acuity (BCVA): 20/20 OD, 20/20 OS
  - No retinal hemorrhages/cotton wool spots OU
  - No evidence of optic neuritis OU
- Macular Optical Coherence Tomography (OCT):
  - OD: normal foveal contour, no intraretinal cysts, central retinal thickness of 319μm
  - OS: few small pericentral intraretinal cysts, approximately 305μm nasal to the foveola, central retinal thickness of 337μm
Assessment: Fingolimod-Associated Macular Edema (FAME), OS only
  o Currently taking fingolimod for MS, initiated 8 months prior

Plan: Due to lack of symptoms and good visual acuity, no treatment was initiated. Continue with fingolimod as directed. Advised patient to return to clinic in 6 weeks for a follow-up examination.

Follow-up for FAME (6 weeks after initial presentation)

Exam Findings:
  o BCVA: 20/20 OD, 20/20 OS (stable)
  o No retinal hemorrhages/cotton wool spots OU (stable)
  o No evidence of optic neuritis OU (stable)

Macular OCT:
  o OD: 1 small pericentral intraretinal cyst, approximately 871μm nasal to the foveola, central retinal thickness of 323μm (increased thickening from previous scan, 6 weeks prior)
  o OS: mildly distorted foveal contour, several large subfoveal & nasal parafoveal intraretinal cysts (largest cyst is approximately 224μm by 156μm), central retinal thickness of 396μm (increased thickening from previous scan, 6 weeks prior)

Assessment: FAME OU
  o Patient has been taking fingolimod for approximately 10 months

Plan: Due to lack of symptoms and good visual acuity, no treatment was initiated. Continue with fingolimod as directed. Advised patient to return to clinic for consultation with the retinal specialist in 3 months.

Neurology Consult (1 month later):

Due to the progressive macular edema likely associated with the use of fingolimod, patient was advised to discontinue the oral fingolimod treatment.

Follow-up Examination for FAME (15 months after initial presentation):

Exam Findings:
  o BCVA: 20/20 OD, 20/20 OS (stable)
  o No retinal hemorrhages/cotton wool spots OU (stable)
  o No evidence of optic neuritis OU (stable)

Macular OCT:
  o OD: normal foveal contour, no intraretinal cysts, central retinal thickness of 288μm (resolved edema, improved from previous scan)
  o OS: normal foveal contour, no intraretinal cysts, central retinal thickness of 298μm (resolved edema, improved from previous scan)

Assessment: Resolved FAME OU
  o Patient had discontinued use of fingolimod 1 year prior

Plan: Monitor annually
III. Differential Diagnosis

- **Primary Diagnosis:** Fingolimod-Associated Macular Edema (FAME)
- **Microcystic Macular Oedema (MMO) associated with Multiple Sclerosis (MS)**
  - Shared characteristics: MMO is reported in 4.7% of patients with MS, can be transient in nature, and can maintain good visual acuity.\(^{19}\)
  - Differentiating characteristics: The appearance of MMO in MS ranges from 20x30\(\mu\)m to 70x90\(\mu\)m in size, and are concentrated within the inner nuclear layers. The microcysts are not generally subfoveal and occur approximately 500-1800\(\mu\)m from the foveal center.\(^{11}\) Fingolimod, however, often leads to a distortion of the normal foveal contour with large sub- and para-foveal cysts and occasionally subretinal fluid. The large, subfoveal cystic spaces on the macular OCT of the patient are more consistent with the presentation of FAME regarding size and location of the macular edema. Although the mechanism of MMO associated with MS may have contributed to the patient’s condition, the time course regarding the appearance and resolution of macular edema in this patient correlates precisely with their concurrent use of fingolimod.

- **Macular Edema associated with Multiple Sclerosis-induced Uveitis**
  - Shared characteristics: Uveitis, such as pars planitis or retinal periphlebitis, is a known ocular complications of multiple sclerosis and may lead to cystoid macula edema (CME) if severe enough.\(^{21}\) The incidence of uveitis in MS patients not treated with fingolimod was similar to the incidence of uveitis in MS patients treated with fingolimod, suggesting the fingolimod use does not increase the risk for uveitis.\(^{23}\)
  - Differentiating characteristics: Despite the inflammatory nature of MS, FAME can occur independent of signs or symptoms of anterior, intermediate, or posterior ocular inflammation. No cells or flare were appreciated on thorough ophthalmoscopic examination of the patient.

- **Macular Edema due to Retinal Vein Occlusion**
  - Shared characteristics: Hypertension and hyperlipidemia are risk factors for the development of retinal vein occlusions, which can lead to retinal thickening and intraretinal fluid and/or blood accumulation.
  - Differentiating characteristics: Vein occlusions have a classic appearance of retinal hemorrhages within the distribution of the occluded vessel and precede the appearance of macular edema. The patient did not have any retinal hemorrhages and only in one case report has FAME presented with an associated macular hemorrhage.\(^2\) Retinal vein occlusions are not traditionally known to be an adverse event of fingolimod use, although two separate cases have been reported.\(^{10,23}\)
IV. Diagnosis & Discussion

- Fingolimod is the first US Food and Drug Administration (FDA)-approved oral agent for the treatment of Relapsing-Remitting Multiple Sclerosis (MS). It is a structural analog of sphingosine 1-phosphate (S1P) that targets S1P1,3-5 receptors throughout the body. 3,6
  - The standard of care may be shifting from weekly, in-office intramuscular interferon beta-1a injections to oral therapies that act to prevent immune-mediated injury, such as fingolimod. 4
- The proposed pathophysiology of macular edema with fingolimod-use is the activation of the S1P receptors on the endothelial cells of retinal capillaries, reducing tight junctions and compromising the blood-retinal-barrier.
  - However, it is currently disputed whether the action on S1P1 or S1P3 receptors, both expressed on the endothelial cells of retinal capillaries is the cause of the leakage. 5,9,12
- Approximately 0.5% of patients taking the FDA-approved dosage of fingolimod (0.5mg/day) develop macular edema 7,13, although this may be an underestimation of the true effect due to infrequent screening and the use of Time Domain – Optical Coherence Tomography (TD-OCT)
- FAME is a dose-dependent response and is predominantly unilateral (75%) 12,18,22
- Fingolimod can also increase macular volume in the absence of cystic spaces, as demonstrated in a study where 74% of eyes of MS patients treated with fingolimod exhibited an increase in macular volume over the course of 5 months, whereas only 37% of eyes of MS patients not treated with fingolimod. 16
- Onset is usually within 4 months of treatment initiation
  - With the earliest reported onset of symptoms at 5 days 15
  - Only a few new onset cases of FAME have appeared 12 months or longer after starting therapy 23
- FAME in patients with diabetes mellitus of a history of uveitis is more commonly bilateral and has more severe visual outcomes 8,12,23
  - The risk of FAME increases to approximately 25% in patients with a history of uveitis 12

V. Treatment & Management

- Discontinuation of fingolimod
  - No additional treatment
    - Approximately 84% had complete resolution (OCT & visual acuity), within 4 months 23
  - Topical anti-inflammatory medications (NSAIDs, corticosteroids)
    - Accelerate complete resolution to within 4 weeks 1
• Continuation of fingolimod
  o No treatment, close monitoring
    ▪ One case study reports stability of macular edema and visual acuity over the course of 25 months since diagnosis without treatment. 14
  o Topical anti-inflammatory medications
    ▪ Can lead to complete resolution (OCT & visual acuity) from case reports 1
    ▪ However, FAME can recur in some patients attempting to taper, eventually requiring the patients to discontinue fingolimod. 14
  o Sub-tenon injection of triamcinolone has been shown to be successful 8,17,20
    ▪ This treatment is generally considered for the patients not responding to the topical anti-inflammatories.

VI. Conclusion
• Onset of FAME is generally within 4 months and resolved without sequelae within 4 months after discontinuation
• Recommended ophthalmologic examinations
  o Baseline before the initiation of fingolimod
  o Follow-up at 4 months, 1 year, and annually thereafter
• Consider more frequent follow-ups in patients with significant risk factors (diabetes mellitus, history of uveitis)
• Every examination must include
  o BCVA
  o Thorough ophthalmoscopy
  o Spectral Domain – Optical Coherence Tomography (SD-OCT)
• Patients can present asymptptomatically
• Topical anti-inflammatories may be effective in patients interested in continuing with fingolimod after developing FAME
BIBLIOGRAPHY: